consolidated into claims 19-26. Claims 29 and 30 have been cancelled as being redundant of pending claims 17 and 18. Applicants reserve the right to prosecute the subject matter of those claims in a separate application, if necessary. Following the amendments, claims 17-26 and 31-36, are pending in the application. Claims 19 and 20 are in independent format. For the Examiner's convenience, the claims have been summarized in Appendix A.

Applicants have amended the claims to more precisely claim the invention. Claims 17-26 and 31-36 have been amended to claim the following Flt3-ligand polypeptides:

- polypeptides comprising amino acids 28-160 of SEQ ID NO:6 that bind flt3 (support may be found, for example, at page 12, lines 9-15);
- polypeptides comprising a fragment of amino acids 28-160 of SEQ ID NO:6, wherein the fragment binds flt3 (support may be found, for example, at page 12, lines 4-15);
- polypeptides comprising a polypeptide that binds flt3 that is at least 90% identical to amino acids 28-160 of SEQ ID NO:6 (support may be found, for example, at page 7, lines 18-35, as well as page 8, line 5 to page 9, line 2); and
- polypeptides comprising a fragment of a polypeptide that is at least 90% identical to amino acids 28-160, wherein the fragment binds flt3 (support may be found, for example, at page 12, lines 4-15, at page 7, lines 18-35, as well as page 8, line 5 to page 9, line 2).

Applicants wish to add claims 31-36, which are drawn to methods of using the compositions of claims 21-26, as permitted under rejoinder. As such, Applicants submit the present claims do not contain new matter and are in condition for allowance.

All pending and newly-added claims enjoy the benefit of parent application U.S. Patent Application Serial No. 08/209,502, filed March 7, 1994. Support may be found, for example, at page 5, lines 10-14 and original claim 63 in the '502 parent application. Applicants note that the particular Flt3-ligand polypeptides presently claimed were also disclosed in the '502 priority application.

Applicants acknowledge that all §102 and §103 rejections have been withdrawn and that these issues have been fully resolved (Final Office Action, paper no. 21, mailed 04/04/2002).

As requested by the Examiner, an updated IDS is filed with this CPA. The *Lyman* reference was cited by the U.S.P.T.O. in U.S. Patent Application Serial No. 08/399,404. The

remainder of the references listed in form PTO-1449 were cited in the International Search Report for the European counterpart of USSN 08/399,404 (EP 95913602.9).

35 U.S.C. §112

Under the Advisory Action, claims 1-8, 17-26, 29 and 30 have been rejected under 35 U.S.C. §112, first paragraph. The Examiner is of the opinion that the specification does not meet the written description and enablement requirements to support the pending claims. Applicants respectfully disagree and present the following remarks in support of the claims.

The U.S.P.T.O.'s Written Description Guidelines permit claiming variants using the "at least X %" language so long as the variants (i.e., species within the genus) possess the specified function (see *Example 14: Product by Function* section of the U.S.P.T.O.'s Written Description Guidelines).

In the application as originally filed, the specification defines the genus of flt3-ligand molecules at page 7, lines 18-31. This definition includes the capacity to bind to the flt3 receptor. Applicants disclose the cDNA and polypeptide sequences for two species- human (SEQ ID NO:6) and murine (SEQ ID NO:2), as well as fragments and variants thereof, that are able to bind a flt3 receptor. Applicants further disclose that this functional activity is essential to the operation of the claimed invention. (See for example, page 7, line 33). Applicants have reduced to practice the two disclosed species and have demonstrated that these species share functional activity, i.e., binding the flt3 receptor.

Furthermore, Applicants disclosed and have reduced to practice several sub-species of the two Flt3-L species, such as the extracellular domain, as well as biologically active fragments of the extracellular domain for SEQ ID NO:6 (for example, see page 12, lines 9-20). The disclosed species and sub-species are representative of the genus because they all possess the required biological activity.

Flt3-ligand variants are defined as polypeptides that are substantially homologous to a native flt3-ligand, but which have an amino acid sequence different from that of native flt3-ligand (human, murine or other mammalian species) because of one or more deletions, insertions or substitutions (page 8, lines 5-8). Notably, the specification states at page 8, lines 8-9 that the variant amino acid sequence preferably is at least 90% identical to a native flt3-ligand amino acid sequence. Applicants' specification teaches procedures for making biologically active variants at page 8, line 5, *et seq.*, as well as in Examples 3 and 4 (beginning at page 29). Also, the specification teaches isolating additional variants by techniques such as cross-species hybridization techniques (see Example 4 at page 34).

Moreover, additional procedures for making variants that have at least 90% identity and retain biological activity are conventional in the art.

The application teaches several assays that may be used to identify flt3-ligand variants having biological activity, i.e., binding to flt3. (See page 16, line 26 to page 19, line 2 for various flt3 binding assays, as well as Examples 10 and 11 for biological function assays).

As such, Applicants respectfully submit that every element of the written description requirements analyzed in Example 14 of the U.S.P.T.O.'s Guidelines have been met by Applicants' disclosure. In light of the above analysis, Applicants respectfully submit that the written description requirements of 35 USC §112 have been fully satisfied for the presently claimed invention.

The test for enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with what is known in the art without undue experimentation. As to what constitutes undue experimentation, a factual determination of the factors described by the *Wands* Court (see, MPEP 2164.01(a)) is to be performed. In short, Applicants submit that one of skill in the art would not have to undertake undue experimentation to make and use the claimed invention because determining flt3-ligand polypeptides that are at least 90% identical to SEQ ID NO:6 is taught in the specification and considered routine in the art and therefore would not constitute undue experimentation.

Applicants define flt3-ligand at page 7 lines 18-31 in terms of polynucleotide and polypeptide sequences from two species that have been reduced to practice (i.e., SEQ ID NOs:2 and 6). Working examples are provided in Examples 1-5. Notably, a key element in determining enablement is whether the starting materials to make the invention are available. This element has been satisfied by disclosure of mouse and human flt3-ligand polynucleotide and polypeptide sequences in the application as originally filed, as well as deposition of flt3-ligand expression vectors with the ATCC. Applicants note that the specification provides direction to one of skill in the art in making flt3-ligand variants that bind flt3 receptor. The specification provides guidance as to which amino acids may be substituted, deleted or inserted, for example, "Variants may comprise conservatively substituted sequences, meaning that a given amino acid residue is replaced by a residue having similar physiochemical characteristics" (page 8, lines 25-27), and, "Examples of conservative substitutions include substitution of one aliphatic residue for another, such as Ile, Val, Leu or Ala for one another, or substitutions of one polar residue for another, such as between Lys and Arg; Glu and Asp;

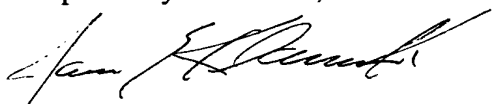
or Gln and Asn. Other such conservative substitutions, for example substitutions of entire regions having similar hydrophobicity characteristics, are well known." (page 8, lines 24-28).

A key factor in this analysis is that the claimed invention is qualified by a functional limitation, i.e. flt3-ligand binding to flt3 receptor. Applicants emphasize that the specification teaches one of skill in the art numerous screening assays by which one may identify functional flt3-ligand variants. See page 16, line 26 to page 19, line 2 for various flt3 binding assays, as well as working examples 10 and 11 for biological function assays. Assays of this sort, especially competitive binding assays, were routinely performed at the time the application was filed and were amenable to large scale screening formats and automation.

Given that the state of the art and the level of ordinary skill are quite high, and that the nature of the invention is such that this type of experimentation is routine, Applicants firmly believe that one of skill in the art would be able to make and use the presently claimed invention using Applicants' original disclosure without undue experimentation. As such, Applicants respectfully request the rejection under 35 U.S.C. §112 be properly withdrawn.

Reconsideration and allowance of the pending claims is kindly requested.

Respectfully submitted,



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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the Application of:
Stewart D. Lyman and
M. Patricia Beckmann

Docket No.: 2813-L

Group Art Unit: 1644

Serial No: 08/994,468

Examiner: P. Gambel

Filed: December 19, 1997

CPA Filed: May 26, 2000

For: MEDIUM CONTAINING FLT3 LIGAND FOR CULTURING HEMATOPOIETIC CELLS (as amended)

Version with Markings to Show Changes

In the specification:

In the "Cross-Reference To Related Applications" at page 1, kindly amend the paragraph as follows:

This application is a continuation of United States Application 08/444,627, filed May 19, 1995, now abandoned, ~~pending,~~ which is a divisional of United States Application 08/243,545 filed May 11, 1994, now allowed and issued as U.S. Patent No. 5,554,512, which is a continuation-in-part of United States Application 08/209,502 filed March 7, 1994, now abandoned.~~, which is a continuation-in-part of United States Application 08/162,407, filed December 3, 1993, now abandoned, which is a continuation-in-part of United States Application 08/111,758, filed August 25, 1993, now abandoned, which is a continuation-in-part of United States Application 08/106,463, filed August 12, 1993, now abandoned, which is a continuation-in-part of United States Application 08/068,394 filed May 24, 1993, now abandoned.~~

In the claims:

The claims have been amended as follows:

Claims 1-8 have been canceled.

17. (Twice Amended) The hematopoietic cells expansion medium of claim 19, further comprising a cellular growth factor.

18. (Twice Amended) The method according to~~of~~ claim 20, ~~wherein the cells are further contacted~~further comprising contacting the cells with a cellular growth factor.

19. (Twice Amended) A hematopoietic cell expansion medium, comprising a cell growth medium and a Flt3-ligand polypeptide in an amount sufficient to cause

hematopoietic cell expansion, wherein the Flt3-ligand polypeptide is selected from the group consisting of:

(a) polypeptides ~~that are at least 90% identical to a polypeptide~~ comprising amino acids 28-160 of SEQ ID NO:6 that bind flt3; ~~and~~

(b) polypeptides comprising a fragment of amino acids 28-160 of SEQ ID NO:6 (a), wherein the fragment binds- flt3;

(c) polypeptides comprising a polypeptide that binds flt3 that is at least 90% identical to amino acids 28-160 of SEQ ID NO:6; and

(d) polypeptides comprising a fragment of a polypeptide that is at least 90% identical to amino acids 28-160, wherein the fragment binds flt3.

20. (Twice Amended) An *in vitro* method for expanding hematopoietic cells, the method comprising contacting the cells with a Flt3-ligand polypeptide in an amount sufficient to cause hematopoietic cell expansion, wherein the Flt3-ligand polypeptide is selected from the group consisting of:

(a) polypeptides ~~that are at least 90% identical to a polypeptide~~ comprising amino acids 28-160 of SEQ ID NO:6 that bind flt3; ~~and~~

(b) polypeptides comprising a fragment of acids 28-160 of SEQ ID NO:6 ~~(a)~~, wherein the fragment binds flt3;

(c) polypeptides comprising a polypeptide that binds flt3 that is at least 90% identical to amino acids 28-160 of SEQ ID NO:6; and

(d) polypeptides comprising a fragment of a polypeptide that is at least 90% identical to amino acids 28-160, wherein the fragment binds flt3.

21. (Twice Amended) The~~A~~ hematopoietic cell expansion medium of claim 19, further comprising ~~a cell growth medium, G-CSF, and a Flt3-ligand polypeptide in an amount sufficient to cause hematopoietic cell expansion, wherein the Flt3-ligand polypeptide is selected from the group consisting of:~~

~~(a) polypeptides that are at least 90% identical to a polypeptide comprising amino acids 28-160 of SEQ ID NO:6; and~~

~~(b) polypeptides comprising a fragment of (a), wherein the fragment binds flt3.~~

22. (Twice Amended) The~~A~~ hematopoietic cell expansion medium of claim 19, further comprising ~~a cell growth medium,~~ GM-CSF. ~~and a Flt3-ligand polypeptide in an amount sufficient to cause hematopoietic cell expansion, wherein the Flt3-ligand polypeptide is selected from the group consisting of:~~

~~(a) polypeptides that are at least 90% identical to a polypeptide comprising amino acids 28-160 of SEQ ID NO:6; and~~

~~(b) polypeptides comprising a fragment of (a), wherein the fragment binds flt3.~~

23. (Twice Amended) The~~A~~ hematopoietic cell expansion medium of claim 19, further comprising ~~a cell growth medium,~~ SF. ~~and a Flt3 ligand polypeptide in an amount sufficient to cause hematopoietic cell expansion, wherein the Flt3 ligand polypeptide is selected from the group consisting of:~~

~~(a) polypeptides that are at least 90% identical to a polypeptide comprising amino acids 28-160 of SEQ ID NO:6; and~~

~~(b) polypeptides comprising a fragment of (a), wherein the fragment binds flt3.~~

24. (Twice Amended) The~~A~~ hematopoietic cell expansion medium of claim 19, further comprising ~~a cell growth medium,~~ EPO. ~~and a Flt3 ligand polypeptide in an amount sufficient to cause hematopoietic cell expansion, wherein the Flt3 ligand polypeptide is selected from the group consisting of:~~

~~(a) polypeptides that are at least 90% identical to a polypeptide comprising amino acids 28-160 of SEQ ID NO:6; and~~

~~(b) polypeptides comprising a fragment of (a), wherein the fragment binds flt3.~~

25. (Twice Amended) The~~A~~ hematopoietic cell expansion medium of claim 19, further comprising a ~~cell growth medium,~~ GM-CSF/IL-3 fusion protein. ~~and a Flt3 ligand polypeptide in an amount sufficient to cause hematopoietic cell expansion, wherein the Flt3 polypeptide is selected from the group consisting of:~~

~~(a) polypeptides that are at least 90% identical to a polypeptide comprising amino acids 28-160 of SEQ ID NO:6; and~~

~~(b) polypeptides comprising a fragment of (a), wherein the fragment binds flt3.~~

26. (Twice Amended) The~~A~~ hematopoietic cell expansion medium of claim 19, further comprising ~~a cell growth medium,~~ IL-6. ~~and a Flt3 ligand polypeptide in an amount sufficient to cause hematopoietic cell expansion, wherein the Flt3 polypeptide is selected from the group consisting of:~~

~~(a) polypeptides that are at least 90% identical to a polypeptide comprising amino acids 28-160 of SEQ ID NO:6; and~~

~~(b) polypeptides comprising a fragment of (a), wherein the fragment binds flt3.~~

Claims 29 and 30 have been cancelled.

Appendix A

CLAIMS FILED WITH CPA March 4, 2003
(Pending claims subject to entry by Examiner Gambel)

17. (Twice Amended) The hematopoietic cells expansion medium of claim 19, further comprising a cellular growth factor.

18. (Twice Amended) The method according to claim 20, further comprising contacting the cells with a cellular growth factor.

19. (Twice Amended) A hematopoietic cell expansion medium, comprising a cell growth medium and a Flt3-ligand polypeptide in an amount sufficient to cause hematopoietic cell expansion, wherein the Flt3-ligand polypeptide is selected from the group consisting of:

(a) polypeptides comprising amino acids 28-160 of SEQ ID NO:6 that bind flt3;
(b) polypeptides comprising a fragment of amino acids 28-160 of SEQ ID NO:6 (a), wherein the fragment binds flt3;
(c) polypeptides comprising a polypeptide that binds flt3 that is at least 90% identical to amino acids 28-160 of SEQ ID NO:6; and
(d) polypeptides comprising a fragment of a polypeptide that is at least 90% identical to amino acids 28-160, wherein the fragment binds flt3.

20. (Twice Amended) An *in vitro* method for expanding hematopoietic cells, the method comprising contacting the cells with a Flt3-ligand polypeptide in an amount sufficient to cause hematopoietic cell expansion, wherein the Flt3-ligand polypeptide is selected from the group consisting of:

(a) polypeptides comprising amino acids 28-160 of SEQ ID NO:6 that bind flt3;
(b) polypeptides comprising a fragment of acids 28-160 of SEQ ID NO:6 , wherein the fragment binds flt3;
(c) polypeptides comprising a polypeptide that binds flt3 that is at least 90% identical to amino acids 28-160 of SEQ ID NO:6; and
(d) polypeptides comprising a fragment of a polypeptide that is at least 90% identical to amino acids 28-160, wherein the fragment binds flt3.

21. (Twice Amended) The hematopoietic cell expansion medium of claim 19, further comprising G-CSF.

22. (Twice Amended) The hematopoietic cell expansion medium of claim 19, further comprising GM-CSF.

23. (Twice Amended) The hematopoietic cell expansion medium of claim 19, further comprising SF.

24. (Twice Amended) The hematopoietic cell expansion medium of claim 19, further comprising EPO.

25. (Twice Amended) The hematopoietic cell expansion medium of claim 19, further comprising a GM-CSF/IL-3 fusion protein.

26. (Twice Amended) The hematopoietic cell expansion medium of claim 19, further comprising IL-6.

Applicants wish to add the following new claims:

31. (New) The method according to claim 20, further comprising contacting the cells with G-CSF.

32. (New) The method according to claim 20, further comprising contacting the cells with GM-CSF.

33. (New) The method according to claim 20, further comprising contacting the cells with SF.

34. (New) The method according to claim 20, further comprising contacting the cells with EPO.

35. (New) The method according to claim 20, further comprising contacting the cells with a GM-CSF/IL-3 fusion protein.

36. (New) The method according to claim 20, further comprising contacting the cells with IL-6.